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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/646,436
Filing Date: August 21, 2003
Appellant(s): GLEAVE ET AL.

Marina T. Larson
For Appellant

SUBSTITUTE EXAMINER'S ANSWER

This is in response to the appeal brief filed May 5, 2010.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Appeal 2009-011955

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 2004/0259247	TUSCHL et al.	12-2004
US 2003/0143732	FOSNAUGH et al.	07-2003

Miyake et al. (Clinical Cancer Research 2000

Hammond et al. RNA Nature Reviews, 2001, Vol. 2, 110-119.

Holen et al. Nucleic Acids Research, 2002, Vol. 30, No. 8: 1757-1766.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The rejection of claims 1, 4, 10, 11, 14, 35 and 36 under 35 U.S.C. 103(a) as being unpatentable over Miyake et al. (Clinical Cancer Research), Tuschl et al. (US 2004/0259247) and Holen et al. (Nucleic Acid Research 2002).

The instant claims embrace dsRNA and are drawn to a RNA molecule having a sequence effective to mediate degradation or block translation of mRNA of a target gene wherein the target gene encodes a clusterin gene and the RNA molecule

comprises a sequence as defined by SEQ ID No. 10 and further drawn to pharmaceutical compositions comprising said RNA molecule together with a pharmaceutically acceptable carrier.

Miyake et al. teach antisense oligonucleotides targeted to clusterin target gene TRPM-2, wherein the antisense oligonucleotide is capable of mediating degradation or blocking translation of the mRNA (see page 1655). Miyake et al. teach prostate cancer is a commonly diagnosed malignancy and TRPM-2 has been found to be unregulated in prostate cancer and acts to inhibit apoptosis of said prostate cancer cells (see abstract and page 1655) and inhibition of TRPM-2 gene using antisense oligonucleotides provides a therapeutic treatment for prostate cancer (see page 1659-1662). Miyake et al. further teach screening active antisense oligonucleotides sequences targeted to the human TRPM-2 gene (see page 1659) and specifically identifies an antisense compound as AS ODN#2 which targets the human TRPM-2 translation initiation site as being capable of reducing TRPM-2 expression (see page 1659) which is the target site targeted by the claimed SEQ ID No. 10 sequence.

At the time of filing of the instant invention, it was well known in the art that RNAi using siRNA was becoming a more efficient method of silencing gene expression. Hammond et al. discusses siRNA and previous methods of reducing using inhibitory molecules such as antisense compounds and states that siRNA is a more potent method of silencing gene expression, requiring only a few molecules of siRNA per cell to silence gene expression (see page 110).

Tuschl et al. teach making and using siRNA for mediating gene silencing (see Example 1 and the siRNA User Guide beginning at paragraph 0178) and has demonstrated siRNA mediated silencing in mammalian cells and states that the use of short siRNAs holds great promise for Inactivation of gene function in human tissues and the development of gene-specific therapeutics (see paragraphs 0144-0151).

Holen et al. teach siRNA efficacy is highly dependent on target position and teach the routine nature of identification of an efficient target site by designing multiple siRNA that overlap in sequence targeted to a known specific target region of a gene (see at least page 1758).

It would have been obvious to one of skill in the art at the time the invention was made to use the methods taught by Tuschl et al. to make a siRNA targeted to a clusterin/TRPM-2 mRNA for the silencing of gene expression.

One of ordinary skill in the art would have been expected to be able to design a siRNA targeted to the same region as the claimed RNA sequence because Tuschl et al. details the steps to effectively find a target site in any RNA and design and test siRNA molecules for specific RNAi activity. Miyake et al. identifies an optimal target region, a region of TRPM-2 gene that is targeted by the claimed SEQ ID No. 10, one of ordinary skill in the art would have been expected to make the claimed RNA molecule comprising SEQ ID No. 10. Moreover, because Holen et al. demonstrates the routine nature of designing siRNA sequence that target a gene every 3 nucleotides, one of ordinary skill in the art would have designed an RNA molecule targeted to TRPM-2 as taught by Miyake et al.

Tuschl et al. teach that it was well recognized in the art that siRNA was a more efficient method of silencing gene expression, requiring concentrations far less than the methods of the prior art, such as antisense compounds. In looking to reduce gene expression of TRPM-2, one of ordinary skill in the art would have wanted use the most efficient method to silencing gene expression and would have looked to the teachings of Tuschl et al. and Holen et al. for generation of siRNAs targeted to of TRPM-2 mRNA. Tuschl et al. and Holen et al. teach that production of siRNAs to any target gene is a matter of routine experimentation and optimization and clearly set forth the guidelines to design such molecules.

Finally, one of ordinary skill in the art would have expected to be able to generate a siRNA targeted to a TRPM-2 gene given Miyake et al. teach an antisense compound targeted to the identical region as the claimed RNA sequence and Tuschl et al. teach the basic steps to identifying any target site and making and screening siRNA molecules for activity, steps that are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 10, 11 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyake et al. (Clinical Cancer Research 2000), Tuschl et al. (US

2004/0259247), Fosnaugh et al. (US 2003/0143732) and Hammond et al. (Nature Reviews 2001, Vol. 2; pages 110-119).

The instant claims embrace dsRNA and are drawn to a RNA molecule having a sequence effective to mediate degradation or block translation of mRNA of a target gene wherein the target gene encodes a clusterin gene and the RNA molecule comprises a sequence as defined by SEQ ID No. 10 and further drawn to pharmaceutical compositions comprising said RNA molecule together with a pharmaceutically acceptable carrier.

Miyake et al. teach antisense oligonucleotides targeted to clusterin target gene TRPM-2, wherein the antisense oligonucleotide is capable of mediating degradation or blocking translation of the mRNA (see page 1655). Miyake et al. teach prostate cancer is a commonly diagnosed malignancy and TRPM-2 has been found to be unregulated in prostate cancer and acts to inhibit apoptosis of said prostate cancer cells (see abstract and page 1655) and inhibition of TRPM-2 gene using antisense oligonucleotides provides a therapeutic treatment for prostate cancer (see page 1659-1662). Miyake et al. further teach screening active antisense oligonucleotides sequences targeted to the human TRPM-2 gene (see page 1659) and specifically identifies an antisense compound as AS ODN#2 which targets the human TRPM-2 translation initiation site as being capable of reducing TRPM-2 expression (see page 1659) which is the target site targeted by the claimed SEQ ID No. 10 sequence.

At the time of filing of the instant invention, it was well known in the art that RNAi using siRNA was becoming a more efficient method of silencing gene expression.

Hammond et al. discusses siRNA and previous methods of reducing using inhibitory molecules such as antisense compounds and states that siRNA is a more potent method of silencing gene expression, requiring only a few molecules of siRNA per cell to silence gene expression (see page 110).

Tuschl et al. teach making and using siRNA for mediating gene silencing (see Example 1 and the siRNA User Guide beginning at paragraph 0178) and has demonstrated siRNA mediated silencing in mammalian cells and states that the use of short siRNAs holds great promise for Inactivation of gene function in human tissues and the development of gene-specific therapeutics (see paragraphs 0144-0151).

Fosnaugh et al. describes making siRNA reagents useful for modulating gene expression. Fosnaugh et al. teach identification of siRNA targets sites in any RNA sequence by screening the mRNA transcript using a computer folding algorithm and describes siRNA that target a gene from a database, such as Genbank (see Example 2). Fosnaugh et al. teach using target sites that are known or have been determined as effective based on studies with other nucleic acid molecules such as antisense can be used to design siRNA as well as target sites known to be associated with disease or conditions such as those containing mutations or deletions (see Example 2). In Example 3, Fosnaugh et al. details selection of siRNA target sites in RNA and screening of siRNA to access activity and teach optimal parameters in designing said siRNA, such as having a GC content preferably 40-60% and comprising 2 nucleotide overhangs. Fosnaugh et al. teach the siRNA molecules are comprised of two strands which are 18 to 24 nucleotides in length (see paragraph 0122) or can be a hairpin structure (see

paragraph 0057) and further comprises nucleotide overhangs (see paragraph 0058). Fosnaugh et al. teach the siRNA can be expressed from expression vectors comprising various promoters such as pol III promoters and termination signals (see paragraph 0220-0223).

It would have been obvious to one of skill in the art at the time the invention was made to use the methods taught by Tuschl et al. and Fosnaugh et al. to make a siRNA targeted to a clusterin/TRPM-2 mRNA for the silencing of gene expression.

One of ordinary skill in the art would have been expected to be able to design any siRNA targeted to any mRNA transcript because Fosnaugh et al. details the steps to effectively find a target site in any RNA and design and test siRNA molecules for specific RNAi activity. Fosnaugh et al. teach known target sites that have previously been targeted by antisense compounds are useful as well as known target sites that have been shown in art to be responsible for certain disease and given Miyake et al. identifies an optimal target region, a region of TRPM-2 gene that is targeted by the claimed SEQ ID No. 10, one of ordinary skill in the art would have been expected to make the claimed RNA molecule comprising SEQ ID No. 10. Moreover, the claimed SEQ ID No. 10 would meet the design requirements as taught by Fosnaugh et al. and Tuschl et al. as discussed above and therefore one of ordinary skill in the art would have designed an RNA molecule targeted to TRPM-2 as taught by Miyake et al.

Both Hammond et al. and Tuschl et al. teach that it was well recognized in the art that siRNA was a more efficient method of silencing gene expression, requiring concentrations far less than the methods of the prior art, such as antisense compounds.

In looking to reduce gene expression of TRPM-2, one of ordinary skill in the art would have wanted use the most efficient method to silencing gene expression and would have looked to the teachings of Tuschl et al. and Fosnaugh et al. for generation of siRNAs targeted to of TRPM-2 mRNA. Tuschl et al. and Fosnaugh et al. teach that production of siRNAs to any target gene is a matter of routine experimentation and optimization and clearly set forth the guidelines to design such molecules.

Finally, one of ordinary skill in the art would have expected to be able to generate a siRNA targeted to a TRPM-2 gene given Tuschl et al. and Fosnaugh et al. teach the basic steps to identifying any target site and making and screening siRNA molecules for activity, steps that are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

(10) Response to Argument

Appellants assert that the key difference between the cited art and the claimed invention is that the sequence of Miyake et al. is a DNA sequence and the claimed sequence is an RNA sequence and although both sequences have the same target site, the claimed sequence includes TT nucleotides at the terminal end which is not taught by Miyake et al.

This argument is not convincing because the cited references provide specific reasons for substituting a dsRNA for an antisense molecule and although the antisense

molecule of Miyake et al. is DNA, its function for reducing a target gene is the same as the function of a dsRNA. As taught by Hammond, siRNA molecules have been found to be a more potent method of silencing gene expression, requiring only a few molecules of siRNA per cell to silence gene expression (see page 110). Tuschl et al. found similar results in that siRNA are more powerful molecules for silencing gene expression and can be used at far lower concentrations that previously known inhibitory nucleic acid molecules such as antisense (see paragraphs 0148 and 0151). Thus a person of obvious skill in the art would have predictably followed the teachings of at least Hammond and Tuschl to use dsRNA for silencing clusterin gene expression given dsRNA are taught to be more desirable molecules to use in RNAi to more efficiently reduce gene expression.

Appellants argue there is no motivation to combine the references Miyake, Tuschl and Holen and has provided no evidence or reasoned argument that a person skilled in the art would ignore the difference in mechanism to predict that a RNA counterpart of a DNA antisense would have activity because Tuschl does not teach targeting an initiation region as claimed and Holen does not teach that DNA antisense sequences are valid starting points for identifying sequences for RNAi.

This argument is not persuasive because Miyake teach antisense oligonucleotides targeted to a clusterin target gene TRPM-2, wherein the antisense oligonucleotide is capable of mediating degradation or blocking translation of the mRNA and states that prostate cancer is a commonly diagnosed malignancy and TRPM-2 has been found to be unregulated in prostate cancer and acts to inhibit apoptosis of said

prostate cancer cells (see abstract and page 1655). Miyake et al. teach inhibition of TRPM-2 gene using antisense oligonucleotides provides a therapeutic treatment for prostate cancer (see page 1659-1662) and teach targeting the translation initiation site of the gene (see page 1659) which is the target site targeted by the claimed SEQ ID No. 10. Thus the motivation is there to reduce expression from this gene and to target the translation initiation site. Given that both Hammond and Tuschl both teach dsRNA as a new more efficient alternative to reducing gene expression, the skilled artisan would have wanted to use the most efficient inhibitory nucleic acid to silencing gene expression of the clusterin TRPM-2 gene. Tuschl teach the basic steps to generating a siRNA, steps that are routine to the skilled artisan and could have predictably been made. Holen teach designing dsRNA molecules along a target sequence and screening these molecules to find the most efficient dsRNA for RNAi. Thus there is an implicit motivation to combine the reference because the combination of references represents an improvement in the field of gene silencing and the combination results in a product that is more desirable because it is more efficient.

Appellant also argues there is no motivation to combine Miyake, Tuschl, Fosnaugh and Hammond to arrive at the claimed invention. Appellants rely on the argument above for not combining Miyake, Tuschl and Hammond and argue that applying the method of Fosnaugh will not allow the skilled artisan to select the dsRNA having SEQ ID No. 10 because this sequence does not meet the requirements of step 7.

This argument is not convincing. As explained above there is implicit motivation to combine Miyake, Tuschl and Hammond. Fosnaugh details in examples 2 and 3, methods of identification of potential siRNA target sites in a RNA sequence. Fosnaugh teach target sites that have been determined to be effective target sites for antisense or ribozyme molecules can be used to design dsRNA molecules and also teach a target site can be separated into subsequences and dsRNA can be made for each subsequence and screened for activity. Given that Miyake identifies a target site and an antisense molecule that is complementary to this site, this target site can be used to make the dsRNA. Fosnaugh teach many alternatives for generating dsRNA and in the alternative method of using subsequences, step 7 teach these subsequences can ranked to see if they contain the dinucleotide UU or AA so as to more readily design dsRNA with terminal TT dinucleotides. Fosnaugh goes on to state that the terminal TT dinucleotides can be added to the dsRNA before synthesizing the oligos. Fosnaugh et al. teach that either the subsequence can have the dinucleotide AA to generate the overhang region or the TT dinucleotide can be added right before synthesis.

As taught by Tuschl the overhang regions is necessary for efficient RNAi and the use of TT as overhang regions is preferably as this reduces the cost of synthesis. Appellant has acknowledged that Miyake teach the identical target region of the claimed SEQ ID No. Thus a person of ordinary skill in the art would have predictably followed the teachings of at least Fosnaugh to generate the dsRNA from a known antisense molecule, in this case the claimed SEQ ID No. 10, as taught by Miyake. Further, a

person of ordinary skill in the art would have followed the teachings of Tuschl et al. and added a dinucleotide thymidine overhang region to improve the efficiency of RNAi.

Therefore, there is a sound basis for combining the prior art references and it would have been obvious to substitute a dsRNA for an antisense molecule in targeting a clusterin gene in an effort to reduce gene expression. Further based on the combination of references, there would have been a reasonable expectation of success at making a dsRNA targeted to the same region as taught by Miyake and comprising TT dinucleotide overhang regions.

Lastly Appellant argues claims 35 and 36 are argued separately as these claims are specifically identified as dsRNA molecules and because Miyake teach DNA, the examiner has not addressed why this change would have been obvious. Appellant's entire argument is based on the use of dsRNA so it is unclear why these claims are argued separately. The cited references provide specific reasons for substituting a dsRNA for an antisense molecule and although the antisense molecule of Miyake et al. is DNA, its function for reducing a target gene is the same as the function of a dsRNA. Double stranded molecules have been found to be a more potent method of silencing gene expression, requiring only a few molecules of siRNA per cell to silence gene expression and are more powerful molecules for silencing gene expression and can be used at far lower concentrations that previously known inhibitory nucleic acid molecules such as antisense. Thus a person of obvious skill in the art would have predictably followed the teachings of at least Tuschl and Fosnaugh to use dsRNA for silencing

clusterin gene expression given dsRNA are taught to be more desirable molecules to use in RNAi to more efficiently reduce gene expression.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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